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Competing Risk Analysis of the Impact of Pedal Arch Status and Angiosome-targeted Revascularization in Chronic Limb Threatening Ischemia

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Key words: angiosome; pedal arch, amputation; competing risk analysis; bypass, percutaneous transluminal angioplasty

Article hightlights

Type of research: Retrospective registry study using competing risk analysis

Key findings: In overall series of 580 infrapopliteal open or endovascular revascularizations, diabetes, rheumatoid arthritis, increased number of affected angiosomes and the absence of a complete pedal arch were independent predictors of major amputation. When patients who underwent bypass surgery and endovascular treatment were analysed separately, it turned out that diabetes was the only risk factor for major amputation after bypass whereas after endovascular revascularization, complete pedal arch and angiosome-targeted revascularization were associated with a lower risk of major amputation.

Take home message: Angiosome-targeted revascularization is important in patients who undergo endovascular revascularization due to EVT especially if pedal arch is incomplete.

Abstract

Introduction: In the context of chronic limb threatening ischemia (CLTI), the prognostic impact of angiosome-targeted revascularization and of the status of the pedal arch are debated.

Materials and method: This series includes 580 patients who underwent endovascular (n=407) and surgical revascularization (n=173) of the infrapopliteal arteries for CLTI associated with foot ulcer or gangrene. The risk of major amputation after infrapopliteal revascularization was assessed by a competing risk approach. A subanalysis was made separately for patients who underwent endovascular or open surgical revascualrization.

Results: At 2 years, survival was 65.1% and leg salvage was 76.1%. Multivariable competing risk analysis showed that C-reactive protein≥ 10 mg/dL, diabetes, rheumatoid arthritis, increased number of affected angiosomes and the incomplete or total absence of pedal arch compared to complete pedal arch were independent predictors of major amputation after infrapopliteal revascularization. Multivariable analysis showed increasing risk estimates of major amputation in patients with incomplete (SHR 2.131, 95%CI 1.282-3.543) and no visualized pedal arch (SHR 3.022, 95%CI 1.553-5.883) compared to complete pedal arch.

Pedal arch was important even if angiosome-targeted revascularization was achieved: Angiosome-directed revascularization in presence of complete pedal arch had a lower risk of

major amputation (adjusted SHR 0.463, 95%CI 0.240-0.894) compared to angiosome-directed revascularization without complete pedal arch.

In the subanalysis, among patients who underwent endovascular revascularization, complete pedal arch (SHR 0.509, 95%CI 0.286-0.905) and angiosome-targeted revascularization (SHR 0.613, 95%CI 0.394-0.956) were associated with a lower risk of major amputation.

Conclusions: Competing risk analysis showed that a patent pedal arch had significant impact on leg salvage and that the subset of patients undergoing endovascular procedure may most benefit of an angiosome-targeted revascularization.

Introduction

Chronic limb threatening ischemia is associated with a high risk of major amputation (1). Subsets of patients with significant comorbidities are also at a formidable risk of early death after lower limb revascularization (2). In this regard, patients' death is a competing risk in the evaluation of the efficacy of leg salvage procedures as the occurrence of mortality after revascularization precludes the ability to observe the outcome of interest (3,4).

The angiosome theory in patients with chronic limb threatening ischemia has been applied in vascular surgery during the last years. Although the results from several retrospective patient series support the angiosome concept, (5,6) the theory has been criticized. The main criticism is that there are several other important factors that have an impact on leg salvage than angiosome concept itself. The importance of angiosome concept and status of pedal arch has been studied earlier in small series where the proper subgroup analyses has not been possible, but they emphasize the importance of complete pedal arch ((7–10).

Thus, in the context of infrapopliteal revascularization for foot ulcer or gangrene, the prognostic impact of angiosome-targeted revascularization approach along with the status of the pedal arch are still debated (9–12). This issue was investigated in this study using a competing risk approach.

Materials and methods

Our vascular surgical centre provides the diagnosis and treatment of CLTI for a population of 1.3 million inhabitants. About 1000 procedures are performed annually for CLTI. Our threshold for

CLTI is a toe pressure ≤30 mmHg in patients without diabetes and ≤50 mmHg in diabetic patients, but all cases with an evident arterial stenosis and poorly wound healing, a revascularization procedure is considered regardless of toe pressure values. The operative techniques offered have been described in detail in previously published articles (13,14).

Patients included in the present analysis were extracted from our prospectively collected vascular registry and it was scrutinized retrospectively regarding all variables included to this study by reviewing patients' case histories and angiograms. External validation of the vascular registry had been done and missing cases added annually. In patients who underwent endovascular treatment, the angiograms before and after the revascularization were reviewed to define whether the procedure was angiosome-targeted or not. In patients undergoing surgical bypass, the pre-operative MRI angiograms and all digital subtraction angiograms were reviewed separately for this analysis. Alltogether 849 patients patients were reviewed, 340 underwent bypass and 508 patients underwent endovascular revascularization. Of these, there were no good quality images on pedal arch in 268 patients (167 bypass patients and 101 endovascular patients). Thus the final number of patients was 580; 173 surgical bypass patients and 407 endovascular patients.

The patency of pedal arch was classified into three categories; complete pedal arch if it was open, incomplete pedal arch when part of the pedal arch was open but it was partially occluded and absent pedal arch, when pedal arch was not visible at all and there were only collaterals at the foot.

The angiosome concept: We defined direct revascularization according to the conventional method used in our earlier publications as a procedure to the artery supplying the angiosome affected by tissue loss, with the exception of lesions located in the forefoot or heel (5, 6). For a tissue defect located in the forefoot, the revascularization of either the anterior tibial/dorsal pedal artery or the posterior tibial artery/plantar arteries were included in the direct group. If the patient's heel was affected, the revascularization of either the posterior tibial or the fibular artery was classified in the direct group. In cases of a tissue loss spread over several angiosomes elsewhere besides the forefoot or heel, we adopted the same approach of direct revascularization as described in the study by Iida et al. – a procedure on the artery supplying the largest surface of the angiosome involved in the lesion (15). If the patient suffered from multiple foot ulcers located in separate angiosomes, all affected angiosomes had to be revascularized in order for the case to be classified into the direct group.

This series includes 580 patients who underwent endovascular and surgical revascularization of the infrapopliteal arteries for chronic limb threatening ischemia associated with foot ulcer or

gangrene from January 2008 to December 2013. Only patients with data on the status of the pedal arch in angiogram were included in the present analysis.

The main outcome endpoint of this series was major lower limb amputation after the index revascularization procedure. Major amputation was defined as any amputation above the ankle level.

Statistical analysis

Statistical analysis performed with Stata version 14.0 statistical software (StataCorp LLC, College Station, TX, USA). Nominal variables were reported as counts and percentages. Continuous variables were reported as mean with standard deviation. Competing risk method was employed because death occurring after the index revascularization procedure is a competing risk, i.e. an adverse event that modifies the chance that major lower limb amputation is required during follow-up. Univariable and multivariable competing risk analysis was performed by including variables of relevance with a $p<0.2$ in the univariable analysis. In any case, the status of the pedal arch and angiosome-targeted revascularization were included in all regression models. Risk estimates are reported as subdistribution hazard ratio (SHR) and 95% confidence interval (CI). A $p < 0.05$ was considered statistically significant.

Results

The baseline characteristics and operative data of the included 580 patients, who underwent either endovascular (n=407) or surgical revascularization (n=173) of the infrapopliteal arteries for CLTI associated with foot ulcer or gangrene, are summarized in Table 1. The mean follow-up of this series was 1.6±1.4 years. At 2 years, survival was 65.1% (no. at risk, 262 patients) and leg salvage was 76.1% (no. at risk, 212 patients). Wound healing at one year occurred in 67.1% of patients (no. at risk, 55 patients).

Multivariable competing risk analysis of the overall series showed that C-reactive protein≥ 10 mg/dL, diabetes, rheumatoid arthritis, increased number of affected angiosomes and the absence of a complete pedal arch were independent predictors of major amputation after infrapopliteal revascularization. Multivariable analysis showed increasing risk estimates of major amputation in patients with incomplete (SHR 2.131, 95%CI 1.282-3.543) and no visualized pedal arch (SHR 3.022, 95%CI 1.553-5.883).

In this series, 324 patients underwent angiosome-targeted revascularization and 100 of them (17.2% of all patients) had a complete pedal arch whereas 224 patients (38.6% of all patients)

had incomplete pedal arch or no pedal arch at all in the angiogram. Competing risk analysis of this subset of patients showed that angiosome-directed revascularization in presence of complete pedal arch had a lower risk of major amputation (SHR 0.463, 95%CI 0.240-0.894) compared to angiosome-directed revascularization without complete pedal arch when adjusted for diabetes, C-reactive protein, rheumatoid arthritis and treatment strategy.

A subgroup analysis of patients who underwent bypass surgery and percutaneous transluminal angioplasty (PTA) was performed and risk estimated of major amputation are summarized in Table. 2. Diabetes was the only predictor of major amputation in patients who underwent surgical revascularization (Tab. 2). Among patients who underwent PTA, C-reactive protein>=10 mg/dL, diabetes, rheumatoid arthritis, the number of angiosomes affected, absence of complete pedal arch and non-angiosome-targeted revascularization were associated with the increased risk of major amputation. The crude and adjusted amputation rate of the patients who underwent non-angiosome targeted endovascular revascularization is presented in the Figure 1.

Discussion

The role of angiosome theory in patients with chronic limb threatening ischemia has been under debate during the last years. Several retrospective trials showed improved wound healing and leg salvage in patients undergoing angiosome-targeted revascularization compared to a non-angiosome-targeted one (5,6). Angiosome theory has been criticized as several other factors are predictors of leg salvage beside the angiosome concept. In the current study we analysed the factors which are possibly related to the outcome of CLTI including the status of pedal arch. We found that in addition to increased C-reactive protein, rheumatoid arthritis and numbers of affected angiosomes, the absence of a complete pedal arch at preoperative angiography was an independent predictor of poor leg salvage. Among patients who underwent targeted revascularization, patients with complete pedal arch yielded lower amputation rate compared to patients without complete pedal arch. Furthermore, angiosome-targeted revascularization was an independent predictor for leg salvage in patients who underwent endovascular revascularization.

The role of pedal arch on the outcome after revascularization has been discussed for a long time, although the quality scientific reports are scarce. Troisi and colleagues (16) studied on the role of pedal arch in 93 diabetic patients with tissue lesion and ischemia after endovascular revascularization of the crural arteries. In their analysis, an angiosome-targeted revascularization did not lead to better wound healing in three months or estimated 1-year

amputation rate, but there was a significant difference in wound healing at three months and estimated 1-year survival between patients with complete pedal arch (wound healing complete pedal arch (CPA) vs. incomplete pedal (IPA) arch vs. absent pedal arch (APA) 46% vs. 13% vs. 21%; 1-year leg salvage 100%, 91% and 76% respectively). However, the number of patients in different pedal arch groups was rather small as there were only 24-40 patients per groups and 13 patients underwent angiosome-targeted revascularization. Furthermore, analysis was not adjusted for other comorbidities. Thus, the findings of this study are conclusive.

According to our results, it seems that the presence of a complete pedal arch is beneficial in terms of outcome of CLTI. These finding couples the results of Higashimori et al. (8), who observed a significantly higher rate of leg salvage in patients with only one vessel runoff can be established to the foot, in whom a direct flow into a patent pedal arch was re-established by endovascular treatment as well as Ricco et al. who found clear association between the existence of pedal arch and limb salvage (3-yr limb salvage after peroneal bypass 73% in patients with complete pedal arch vs. 46% in patients with incomplete pedal arch)(10). In our series, angiosome-targeted revascularization yielded to better leg salvage than non-angiosome-targeted one, and the open pedal arch increased the leg salvage even further among those patients who received angiosome-targeted procedure. This finding is not surprising as a complete pedal arch results in to a better outflow and better circulation to the skin and wound area. A minority of patients with CLTI have complete pedal arch. In our series, this was the case in 28% of the patients. In a study with 125 CLTI limbs, a complete pedal arch was observed only in 18% of cases, However, this study included only patients who had incompressible crural arteries (ABI>1.4). It is controversial whether the recanalization of an incomplete or absent pedal arch leads to better outcome. Several studies reported on endovascular recanalization of a pedal arch even in cases where it has been totally occluded (14,15). The immediate technical success has been satisfactory, however no long term patency or outcome data is available.

In our earlier study with 545 patients with diabetes and ischemic tissue lesion, we analysed the importance of angiosome concept in both surgical and endovascular revascularization. We found that in patients who underwent surgical bypass, there was no significant difference between patients who underwent angiosome-targeted bypass versus non-targeted one. However, after endovascular revascularization, the outcome was clearly better after the targeted PTA compared to non-targered one. This finding was also noted in our series of 700 patients with CLTI and tissue lesion with or without diabetes (5). In published meta-analyses on angiosome concept this difference between surgical and endovascular revascularization has not been verified, however the number of surgical patients in these has been relatively low and majority of them do not separate revascularization mode. In the current study we analysed separately the

predictors for the favourable outcome for surgical and endovascular patients. First of all, there was no difference between surgical and endovascular revascularization in limb salvage. Surprisingly, diabetes was the only independent factor associated with the major amputation after surgical bypass, whereas after endovascular revascularization, there were several independent risk factors for leg salvage, for example angiosome-targeted revascularization, complete pedal arch and small number of affected angiosomes. Of course the power of subanalysis is limited by the small number of patients who underwent bypass surgery. The reason for significantly lower number of bypass patients was the fact that there was no imaging of pedal arch in many patients who underwent bypass surgery on the basis of MRI in which the visualization of pedal arch was compromised. However, our results are in line with the results from Ricco and colleagues who analysed 120 patients who underwent peroneal bypass due to CLTI: they did not find association between limb salvage and angiosome targeted bypass after bypass surgery. In turn, patent pedal arch predicted better leg salvage. (10)

Rheumatoid arthritis had strong independent association with poor leg salvage. There are very few studies that have examined the clinical outcome of patients with both lower limb arterial disease and rheumatoid arthritis (16,17). Wound healing studies suggest that the wound healing is compromised due to altered skin compression and immunosuppressive agents and that atherosclerosis progression may be accelerated in patients with RA (16). In a very small study with only 41 RA patients of which one third had claudication and two third had rest pain or ischemic ulcer, 25 bypass operations were done during 5 year period. Six patients sustained amputation and the authors concluded that the patients who have RA and LEAD, same indications should be kept for revascularization than in patients without RA. However, further studies are needed to better evaluate the prognostic impact of rheumatoid arthritis in patients with lower limb ischemia. Meanwhile, we recommend to have low threshold for revascularization pa RA patients with tissue lesion and more close follow-up after revascularization.

The present results should be viewed in light of some limitations. First, the retrospective nature of this study might hinder the risk of a bias in the collection of data on the severity of lower limb ischemia, the degree of infection and the extent of foot lesions. Second, the revascularization method and the decision on angiosome-targeted strategy were based on the anatomical pattern and extent of atherosclerosis disease and the feasibility of the revascularization procedure. Third, angiosome-directed revascularization approach may be less effective in presence of foot lesions involving multiple angiosomes and render difficult the analysis of these prognostic factors. Finally, the small size of patients in the surgical revascularization cohort prevented conclusive results on the determinants of major amputation in this subset of patients. Therefore,

the results of the competing risk analysis in the overall series mostly reflect the results of the PTA cohort as suggested by similar risk estimates (Tabs. 1-2). Also the lack of WIfI classification is a limitation as it would give valuable information on the amputation risk. However, we do have infection and extend of tissue lesion (number of affected angiosomes) on our multivariable analysis. Only the ABI or toe pressure is missing as the data regarding the hemodynamic values is incomplete.

Conclusions

Competing risk analysis confirmed that the extent and severity of infection of the ischemic foot lesions are independent predictors of major lower limb amputation along with diabetes and rheumatodid arthritis. Competing risk analysis showed also that a patent pedal arch had significant impact on leg salvage and that the subset of patients undergoing endovascular procedure may most benefit of an angiosome-targeted revascularization.

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345 **Table 1.** Risk estimates of major amputation in competing risk analysis.

		Major amputation	
Baseline covariates	*No. (%) / mean (SD)*	*Univariate analysis p-value*	*Multivariate analysis SHR, 95%CI*
Age	74.0 (11.5)	0.369	
Female gender	213 (36.7)	0.791	
C-reactive protein ≥10 mg/dL	363 (62.6)	0.001	2.030, 1.267-3.253
eGFR (mL/min/1.73 m^2)	76.9 (36.9)	0.864	
Dialysis	33 (5.7)	0.647	
Diabetes*	401 (69.1)	0.010	1.984, 1.249-3.153
Coronary artery disease*	204 (35.2)	0.747	
Heart failure	71 (12.2)	0.848	
Stroke	78 (13.4)	0.986	
Smoker*	83 (14.3)	0.110	
Pulmonary disease*	57 (9.8)	0.096	
Rheumatoid arthritis	37 (6.4)	0.010	2.310, 1.348-3.959
Gangrene	153 (26.4)	0.604	
No. of angiosomes affected	2.2 (0.9)	<0.0001	1.289, 1.069-1.554
Complete pedal arch	160 (27.6)	0.002	0.447, 0.271-0.738
PTA vs. bypass surgery	407 (70.2)	0.933	
Angiosome-targeted revascularization	324 (55.9)	0.476	

346 SHR: subdistribution hazard ratio; CI: confidence interval; PTA: percutaneous transluminal angioplasty; eGFR:
347 estimated glomerular filtration rate. (*Diabetes=Diabetes medication or diagnosed diabetes with diet therapy;
348 Coronary artery disease=CABG, PCI or AMI in history, angina pectoris or ischemia in EKG; Smoker=active smoker or
349 quitted less than 5 years ago; Pulmonary disease=diagnosed COPD or asthma)

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352

353 **Table 2.** Risk estimates of major amputation according to treatment method in competing risk
354 analysis.

Covariates	*Multivariate analysis SHR, 95%CI*
Bypass surgery	
Diabetes	2.581, 1.030-6.470
PTA	
Angiosome targeted revascularization	0.613, 0.394-0.956
Complete pedal arch	0.509, 0.286-0.905
C-reactive protein ≥10 mg/dl	2.200, 1.106-3.233
Diabetes	1.891, 1.106-3.233
Rheumatoid arthritis	2.553, 1.416-4.601
No. of angiosomes affected	1.366, 1.103-1.691

355 SHR: subdistribution hazard ratio; CI: confidence interval; PTA: percutaneous transluminal angioplasty.

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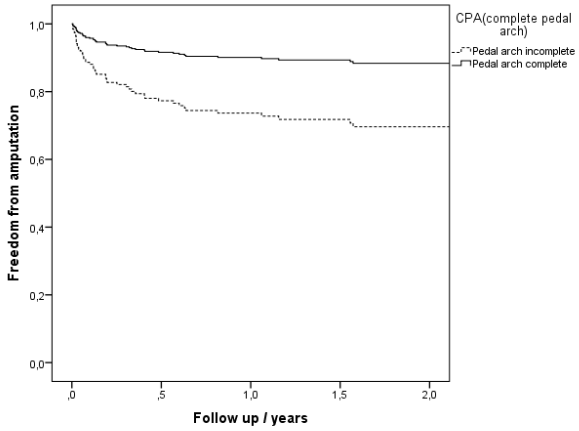
359 Legend of the Figure 1

360

361 Leg survival in patients who underwent non-angiosome targeted endovascular
362 revascularization (n=192) adjusted with diabetes, number of affected angiosomes, CRP,
363 rheumatoid arthritis.

364

365


CPA(complete pedal arch)
Pedal arch incomplete
Pedal arch complete
Freedom from amputation
1,0
0,8
0,6
0,4
0,2
0,0
,0
,5
1,0
1,5
2,0
Follow up / years